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Polypharmacy for Schizophrenia

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Abstract

Purpose of review—Combining psychotropic medications is common for people diagnosed with schizophrenia facing a variety of clinical circumstances. This review provides an update on evidence regarding the effectiveness of polypharmacy approaches.

Recent findings—Epidemiology studies have demonstrated that polypharmacy is extremely common but evidence regarding all polypharmacy approaches for schizophrenia from randomized controlled trials remains scarce. Combinations of antipsychotic medicines are unsupported by evidence. Antidepressants are commonly used to treat depressive symptoms; this logical role for antidepressants has little support from RCTs but may be associated with lower suicide and all-cause mortality. No evidence supports the use of benzodiazepines for schizophrenia; possible risks of benzodiazepines including increased mortality rates revealed in observational studies warrant caution and further study.

Summary—The lack of evidence regarding common treatment strategies exacerbates the tremendous challenge of providing optimal pharmacotherapy for individuals with schizophrenia. Comparative effectiveness research, using observational methods when appropriate and randomized controlled trials when possible, is needed to inform clinical practice, use resources wisely, and improve outcomes.

KEY PHRASES

polypharmacy; schizophrenia; pharmacoepidemiology; randomized controlled trial; treatment refractory

Introduction

Identifying optimal treatments for individuals diagnosed with schizophrenia remains challenging. Despite the availability of a large number of antipsychotic agents, achieving the therapeutic goals that are important to patients is all too rare. A reduction of positive symptoms is the standard measure of therapeutic efficacy for schizophrenia treatments, not coincidentally because antipsychotics are most effective for these symptoms. But this marker of treatment success leaves much to be desired because other symptoms of

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schizophrenia and comorbidities are often present and contribute to distress and disability. In fact, negative symptoms and cognitive symptoms have the greatest impact on overall functioning among individual with schizophrenia, yet there are no proven pharmacological strategies that improve these symptoms. Unfortunately there is little evidence to guide decision-making for situations beyond the core psychotic symptoms.

Schizophrenia that is unresponsive to treatment

Stakeholders including patients, clinicians, and researchers who recently collaborated to identify the ten most important questions about schizophrenia treatment concluded that schizophrenia that is “unresponsive to treatment” is the most pressing issue facing schizophrenia researchers.[1] Though numbers depend on what is meant by “responsive”, a substantial proportion of people with schizophrenia are unsatisfied with treatment outcomes. [2] Up to 70% of patients do not achieve full remission, even when taking antipsychotic medications as recommended.[3]

Combinations of antipsychotics are commonly used in schizophrenia when a single agent does not relieve symptoms adequately. In a recent meta-analysis, Correll and colleagues presented findings arguing that antipsychotic polypharmacy may have a clinical advantage over standard (non-clozapine) monotherapy in non-responsive patients. While the overall results may offer some support for antipsychotic combinations, the finding diminishes significantly if studies from China are removed, and thus the generalizability of those findings is questionable. Benefits of antipsychotic combinations were also not seen in short-term studies, which points to the need for more long-term trials of this strategy. [4] However, clozapine remains the only proven treatment for patients who do not respond fully to other antipsychotics. Despite this knowledge, clozapine uptake is low in most communities. No randomized clinical trial has directly compared clozapine to combinations of antipsychotics.

Essock and colleagues took advantage of the fact that combinations of antipsychotics are common in clinical practice by conducting a trial that randomized people who were stable on a combination of two antipsychotics to either discontinue one of the antipsychotics or to continue on both. [cite 9 here] They found that dropping one antipsychotic was associated with fewer side effects but that more patients assigned to stay on two antipsychotics stayed in the assigned condition than stayed in the switch to monotherapy condition. People who did not stay in the monotherapy condition typically resumed the previous combination of antipsychotics. Overall, people assigned to the switch to monotherapy condition did not experience more symptoms or hospitalizations.[5] The authors acknowledged that this study did not address the issue of whether initiating combinations was effective, but concluded that a switch to monotherapy for people taking two antipsychotics may well have benefits that exceed risks.

Despite clozapine’s superiority for refractory symptoms, even when it is used clozapine is not effective for every patient with treatment-resistant schizophrenia. A major issue is that the drug’s side effects can be limiting, and for at least one third of patients clozapine is discontinued within the first year of treatment.[6, 7] Because clozapine is the last step on

evidence-based treatment algorithms, this presents a problem when further strategies are needed. Evidence to guide treatment decisions when clozapine fails is notably limited. Many consider trying previous antipsychotic medications at higher doses, others use long-acting agents, and many consider augmenting clozapine with an additional psychotropic.

A Cochrane review of combining antipsychotics with clozapine for treatment-resistant schizophrenia found only small trials that were inconclusive (Cipriani et al 2010). More recently, clozapine augmentation with aripiprazole[8] showed benefit on PANSS scores but did not demonstrate benefits in cognitive measures. Similar benefit was also seen with duloxetine in a study by this same group[9], but not with topiramate.[10] There remains no clear recommendation for how to augment clozapine or what other strategies to employ when an individual does not tolerate or respond meaningfully to clozapine.

Targeting Nonpsychotic Symptoms

The core positive and negative symptoms of schizophrenia are rarely the only targets for treatment. Mood, anxiety, and obsessive-compulsive symptoms frequently require attention but evidence for how best to approach these comorbidities is scant (see table 1).

A parsimonious approach is to begin by optimizing antipsychotic monotherapy and psychosocial supports. An obvious but unproven approach is to treat these problems symptomatically by using treatments proven effective for mood and anxiety disorders. However, the need for internal validity when seeking regulatory approval for new medications leads to excluding people with comorbidities from clinical trials. For example, because people with schizophrenia are systematically excluded from trials of putative antidepressants and anxiolytics the results of these trials only clearly apply to people without schizophrenia.

Whether the conventional treatments for common clinical symptoms such as depressed mood or anxiety are similarly effective for people with schizophrenia is not clear. Treating mood symptoms for example, is particularly difficult in schizophrenia. Differentiating between negative symptoms and depression is clinically challenging and though there may be phenotypic overlaps it is not known precisely what the pathophysiological differences are, and how those differences may affect the benefits of certain medications.

Although antipsychotic medications reduce ratings of negative symptoms, this benefit is thought primarily to result from improvement of secondary negative symptoms and a resulting decrease in social withdrawal. In the absence of proven treatments for primary negative symptoms, or those that do not improve with antipsychotic treatment alone, antidepressants are often considered for use. Evidence is varied on the effectiveness of antidepressants for negative symptoms. In a meta-analysis, a modest effect size of 0.48 was shown overall in favor of using antidepressants, though with the removal of three outlier results, the effect size dropped to 0.33.[19] Notably in this meta-analysis more studies showed inconclusive benefit than showed statistically significant benefits for antidepressants. Moreover, the only commonly used antidepressant to show a benefit was fluoxetine (trazodone and ritanserin also were statistically significant in one study each) and did so in only 1 of 4 reported trials. Other antidepressants failed to show a distinct and

significant benefit when data were combined.[19] A study of escitalopram conducted after the above systematic review also failed to demonstrate substantial benefits.[20] A single small study using mirtazapine demonstrated small benefit for mirtazapine on negative symptoms, but subjects gained more than 5 kg compared to those on placebo.[21]

Antidepressants may yield benefits beyond direct symptomatic improvements in people diagnosed with schizophrenia. A recent pharmacoepidemiology study from Finland found antidepressants to be associated with decreased mortality. The finding appears to extend beyond just decreased suicide rates. In the same study, benzodiazepines were associated with increased mortality, which was also not related to increased suicide rates. The findings of this observational study require replication and need to be understood in the context of possible confounds, but highlight the significant impact, positive and negative, that additional medications may have in addition to measurable symptom differences.[22]

Benzodiazepines are frequently used to target symptoms, including anxiety and insomnia. While rates of benzodiazepine augmentation likely vary around the world, a recent report from Taiwan indicated that nearly 80% of schizophrenia patients were receiving benzodiazepines over the course of one year.[23] Small area variations likely would demonstrate that the rates vary widely even within close geographic areas, though that data remains to be fully described for people with schizophrenia.[24] The significant variations in use highlight the lack of evidence-based recommendations regarding benzodiazepines. The most recent systematic review data from the Cochrane group does not find evidence that benzodiazepines are useful beyond short-term sedation in schizophrenia.[14] However, the lack of evidence in support of benzodiazepines does not rule out their use, as there are circumstances and individuals in which they can be helpful. The recent adverse mortality data, however, should be considered when using benzodiazepines particularly if for more than short-term treatment.

The use of anticonvulsants, either to potentiate the effect of antipsychotic medications, or to help prevent mania has a long and complicated history. Valproic acid is sometimes used to accelerate the response to antipsychotics.[25] While helpful in the acute situation there is no demonstrated benefit to this strategy after six months.[15] This leads to the common polypharmacy scenario in which the regimen is no longer supported by research evidence, but unless the patient is demonstrating side effects or other reasons to discontinue the treatment, a regimen that was apparently beneficial acutely is continued indefinitely. While seeming innocuous, maintaining unnecessary medications exposes the patients to the potential for side effects on a treatment regimen with unclear benefit.

Lamotrigine is seen as an adjunctive medication for schizophrenia due to its mood elevating properties. There have been few controlled studies of lamotrigine in schizophrenia other than for patients who did not respond fully to clozapine. In a recent meta-analysis, it was concluded that lamotrigine did not do better than placebo as a clozapine-augmentation strategy.[26] Smaller studies have focused on topiramate. Initial reports show little benefit on topiramate on positive or negative symptoms. Cognitive side effects are common with topiramate and thus further limit its clinical utility.[10]

Targeting Side Effects

Among the greatest difficulties in treating schizophrenia is that the most effective antipsychotic medications, olanzapine and clozapine, are also associated with the greatest risk for metabolic side effects.[27] A treatment that maximized the antipsychotic effects of these medications but did not expose patients to metabolic risk would be ideal. Polypharmacy approaches overall have been shown to contribute towards the risk of metabolic syndrome[28, 29]. Often tolerability issues drive the need to combine antipsychotics.[30] To minimize side effects, lower doses of individual antipsychotic medications are often utilized. While there is a basis for dose-dependence in the development of extrapyramidal symptoms, this has not been conclusively established with metabolic side effects of second-generation antipsychotics.[31]

Some have thought that a more specific approach to achieve this goal is to use a minimal but effective dose of clozapine, while potentiating its effect with an adjunctive medication that acts mechanistically different. The most studied version of this strategy uses aripiprazole as the adjunctive agent. Aripiprazole is an attractive agent for this purpose because it causes relatively little sedation and weight gain. In a double-blind placebo-controlled trial, those assigned to aripiprazole augmentation lost an average of 3kg (vs 0.5kg in the placebo group) over 8 weeks. After an open-label extension, the weight loss was maintained at 28 weeks.[32] However, a randomized study comparing clozapine augmentation with aripiprazole to haloperidol found no advantage for aripiprazole on duration of treatment or symptoms, although patients perceived aripiprazole as more tolerable.[33]

There are few weight loss agents available on the market, and thus far none of them have been shown effective in use in schizophrenia either because of lack of efficacy or unacceptable side effects.[34, 35] While not a weight loss agent per se, topiramate's weight loss properties are often sought to help mitigate side effects of high metabolic risk antipsychotics. In a recent study from India (n=67), drug-naïve first-episode subjects randomized to topiramate plus olanzapine lost 1 kg over 12 weeks compared to those only on olanzapine who gained an average of 6 kg.[36] Zonisamide was also used in a study to try to prevent olanzapine induced weight gain. While subjects gained slightly less weight with zonisamide, like topiramate, the effect is limited by cognitive side effects. In this study, 25% had cognitive side effects while on zonisamide, compared with 0% on placebo.[37] A study conducted by the NIMH-sponsored Schizophrenia Trials Network found that metformin was well tolerated and modestly effective in reducing weight in overweight or obese patients with chronic schizophrenia taking any one or two antipsychotics.[38] A meta-analysis of four previous studies also found improvements in weight gain, glucose, and waist circumference in people who took metformin concurrent with olanzapine.[39]

Future Directions and Conclusions

Treatment of individuals with schizophrenia who have complicated courses of illness, particularly those who do not benefit adequately to antipsychotic monotherapy, remains beyond the current state of evidence-based practice. Algorithms that are based on research evidence are often unable to provide specific recommendations. When clozapine is not an

option, or has not worked, evidence for various treatment options is scarce. Many wish to try regimens that combine antipsychotics with different purported receptor mechanisms. While this technique makes sense in an in-vitro model, it presupposes that schizophrenia can be fixed by fine-tuning the activity at these receptors. Unfortunately this “jigsaw puzzle” approach has not been shown to be of benefit, though limitations in clinical trial methods and capabilities have hampered developing a strong evidence base for different treatment combinations. One practical approach to combining antipsychotics if this approach is attempted is to avoid drugs with similar side effect profiles to avoid additive adverse effects.

The need to make treatment decisions in the absence of guiding evidence is common for all clinicians. When treating individual patients in situations of uncertainty, the patient’s history and preferences are primary considerations. Combinations of psychotropic medications may be necessary and beneficial, but should be undertaken carefully with the understanding that evidence supporting even common polypharmacy practices is weak at best. Clinicians should carefully monitor for additive side effects and added drugs that do not improve target symptoms should be discontinued.

Research will never be able to address every clinical scenario, but the future of clinical research in schizophrenia must allow for more broad conclusions to be drawn. Current clinical trial models emphasize internal validity, often at the cost of external validity. Rigid designs that limit the types of augmentation agents or baseline antipsychotics limit generalizability of overall findings. Pragmatic clinical trials, which emphasize external validity through more real-world entry criteria, are expensive and require substantial sample sizes to overcome the need for greater power to achieve significant results. Despite these limitations, further development in clinical trial design is critical for developing rational treatments for these commonly vexing clinical situations. Observational comparative effectiveness methods using large databases can begin to answer many of these questions but in some cases confounding means that only randomized trials will yield reliable results.

In conclusion, many schizophrenia treatment decisions are not adequately informed by research. Polypharmacy approaches are often reasonable strategies, but should be undertaken with the knowledge that these are not evidence-based practices. As with any new medication strategy, target symptoms and treatment goals for any added psychotropic should be identified and adverse effects monitored. If the desired benefits of an additional medication are not realized, or if adverse effects exceed benefits, the new drug should be discontinued.

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Key Points

- Treatment of schizophrenia requires consideration beyond improvements in positive symptoms.
- There is limited evidence to support using multiple antipsychotic medications concurrently.
- There is limited evidence to support using SSRIs, benzodiazepines, or anticonvulsants as long-term adjunctive agents in schizophrenia.
- Pragmatic clinical trials and other forms of comparative effectiveness research should incorporate multiple outcomes to guide future care decision.

Table 1

Summary statements of systematic reviews of antipsychotic augmentation

	Cochrane Reviews ⁽¹⁾	Schizophrenia PORT ⁽²⁾
Antidepressant	Inconclusive evidence on use of antidepressants for depression or negative symptoms in people with schizophrenia.[11, 12]	Possibly effective for post-psychotic depression; not enough evidence to support a recommendation for negative symptoms.[13]
Anxiolytic	Inadequate evidence to recommend benzodiazepines either as a sole or adjunctive agent in schizophrenia.[14]	Insufficient evidence to make a recommendation.[13]
Antimanic	Reviews found inadequate evidence to recommend augmentation of antipsychotics with valproate [15], Lamotrigine[16], Carbamazepine[17], Lithium[18]	None with sufficient evidence to warrant a recommendation.[13]

(1) Cochrane Collaboration Systematic Reviews are meta-analyses based on evidence from randomized controlled trials.

(2) The Schizophrenia Patient Outcomes Research Team (PORT) systematically reviews evidence on treatments for schizophrenia and synthesizes this information; when evidence is sufficient the PORT makes a treatment recommendation.